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Viewpoint

# Current Risk of Contrast-Induced Acute Kidney Injury After Coronary Angiography and Intervention: A Reappraisal of the Literature

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## ABSTRACT

**Contrast-induced acute kidney injury (CI-AKI) is the acute impairment of renal function further to the intravascular administration of iodinated contrast media, and occurs most frequently after coronary angiography, percutaneous coronary intervention, and contrast-enhanced computed tomography. CI-AKI has been associated with the development of acute renal failure, worsening of chronic kidney disease, requirement for dialysis, prolonged hospital stay, and higher mortality rates and health care costs. Recently, a number of studies suggested that contrast media exposure might not be the causative agent in the occurrence of acute kidney injury, particularly in stable patients who receive small to moderate amounts of contrast media. However, those who undergo coronary angiography and intervention are indeed subject to an increased hazard of CI-AKI, in view of a more significant contrast media exposure as well as the presence of concomitant risk factors. Solid randomized clinical trials are therefore required to identify preventative strategies to reduce the risk of CI-AKI and its complications in these patients.**

## RÉSUMÉ

**L'insuffisance rénale aiguë induite par les produits de contraste (CI-AKI, de l'anglais *contrast-induced acute kidney injury*), qui est la détérioration de la fonction rénale à court terme à la suite de l'administration intravasculaire d'un produit de contraste iodé, apparaît le plus souvent après l'angiographie coronarienne, l'intervention coronarienne percutanée et la tomodensitométrie rehaussée par un agent de contraste. La CI-AKI a été associée au développement de l'insuffisance rénale aiguë, à la détérioration de la maladie rénale chronique, au besoin de dialyse, à des séjours prolongés à l'hôpital et à des taux de mortalité et à des coûts des soins de santé plus élevés. Récemment, plusieurs études ont permis de croire que l'exposition aux produits de contraste ne serait pas le facteur causal de la survenue de l'insuffisance rénale aiguë, particulièrement chez les patients ayant un état clinique stable qui reçoivent des quantités faibles ou modérées de produits de contraste. Toutefois, ceux qui subissent une angiographie coronarienne et une intervention coronarienne sont en fait exposés à une augmentation du risque de CI-AKI compte tenu d'une exposition plus importante aux produits de contraste et de la présence de facteurs de risque concomitants. Par conséquent, des essais cliniques à répartition aléatoire fondés sont nécessaires pour trouver des stratégies préventives qui réduiront le risque de CI-AKI et ses complications chez ces patients.**

In this article, we provide a critical review of the recently published literature challenging the association between contrast media administration and contrast-induced acute kidney injury (CI-AKI) development. Additionally, we review the pathogenesis of acute kidney injury (AKI) in the context of coronary angiography and intervention. Finally, we stress the importance of intravascular volume expansion to minimize the risk and effects of CI-AKI.

## CI-AKI: Definition of the Problem

CI-AKI is defined as the occurrence of acute renal impairment after administration of iodinated contrast media, which exert nephrotoxic effects by means of vasoconstriction, oxidative stress, osmotic tubular nephrosis, and ischemia of the outer medulla.[1] Most CI-AKI cases stem from intravascular contrast media exposure during coronary angiography, percutaneous coronary intervention (PCI), and contrast-enhanced computed

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tomography imaging.[2] Traditionally, CI-AKI has been reported as one of the leading causes of acute renal failure during hospitalization,[2] and is associated with progression of renal failure, requirement for dialysis, prolonged hospital stay, mortality, and increased costs.[1,3-5] However, recent publications have challenged these associations, and some researchers have called for a reappraisal of the actual role of contrast media in the development of AKI and its effect on clinical outcomes.

## Does CI-AKI Really Exist?

Recent studies reported a low incidence of CI-AKI (2.4%-6.4%) in patients who underwent intravenous contrast media administration for computed tomography imaging.[6,7] In several studies, McDonald et al.[7-9] analyzed the risk of CI-AKI and its effect on outcomes in patients who underwent computed tomography imaging with or without contrast media administration. After propensity score adjustment, the authors reported that AKI risk was similar between contrast- and non-contrast-enhanced scans, across all risk subgroups.[9] These data suggest that critically ill patients who undergo computed tomography imaging might have other causes of AKI and that contrast media might not be the causative agent. Additionally, intravenous contrast media administration was not associated with higher 30-day mortality or need for dialysis. Although patients who developed AKI suffered higher rates of dialysis and mortality, contrast media exposure was not an independent predictor of either outcome, even among subjects with chronic kidney disease (CKD) or other predisposing comorbidities.[8]

Similarly, a recent report on 6 million hospitalizations showed no difference in the incidence of CI-AKI between patients exposed to and those not exposed to contrast media (5.5% vs 5.6%).[10] This cohort included subjects who underwent contrast media exposure in different settings and for a wide variety of conditions. The risk of AKI increased with a higher comorbidity burden in both groups. After adjustment for comorbidity and clinical presentation, contrast media administration was paradoxically associated with a 7.4% *reduction* in AKI odds. The authors concluded that the relationship between contrast media administration and AKI is highly confounded, unpredictable, and might express a risk-treatment paradox ("renalism"[11]). In particular, among patients with acute coronary syndrome (ACS), subjects with CKD undergo coronary angiography and intervention significantly less frequently than non-CKD patients, because of an aversion to the risk of CI-AKI, despite the fact that they would benefit the most from revascularization.[12] Crucially, these patients—who are not exposed to contrast media—still suffer higher rates of AKI (because of the direct consequences of an unrevascularized ACS on kidney function), compared with subjects who undergo an invasive management and thereby are exposed to contrast media.[8]

This body of evidence might suggest that contrast media administration might not be the causative agent of increased creatinine values, and might not be associated with a higher risk of AKI, dialysis, or death, even among subjects with comorbidities predisposing to nephrotoxicity.[8,9] To further support this hypothesis, the authors[10] point out that, during hospitalization and in the absence of contrast media exposure, patients' serum creatinine levels might fluctuate significantly, often exceeding thresholds considered diagnostic of CI-AKI.[13] Therefore, in a relevant proportion of cases, development of AKI might be pathophysiologically unrelated to earlier (incidental) contrast media exposure. Interestingly, the same conditions considered to be CI-AKI risk factors (eg, age, diabetes, advanced CKD, heart failure, hemodynamic instability, etc) also represent risk factors for AKI in general (contrast media-unrelated), which might therefore be mediated through alternative pathways.

The authors of the aforementioned reports[7-10] conclude that the incremental risk of AKI that can be attributed to contrast media is modest and probably overestimated.[10] However, these studies present important limitations, namely their observational nature and their "big data approach." Because the authors relied on administrative discharge summaries to adjudicate AKI events, they could not capture variables of critical importance such as the volume of contrast media administered, laboratory exams (including serum creatinine values), and the temporal sequence between contrast media administration and AKI development, thus losing precision in the assessment of such a complex phenomenon. As a consequence, their findings and conclusions should be regarded with caution, because they do not provide any definitive evidence of the lack of association between contrast media exposure and subsequent AKI.

## CI-AKI in Patients Who Undergo Coronary Angiography and Intervention

Another important limitation of the aforementioned reports is represented by the fact that most of their data come from populations that underwent noninvasive procedures, and high-quality data specific to a population that underwent coronary angiography and intervention are scarce.

The incidence of CI-AKI is somehow higher after coronary angiography and intervention (7.1%-10.5%[14,15]), compared with computed tomography imaging (2.4%-6.4%[6,7]), a finding that can be explained by differences in baseline characteristics and clinical presentation between the 2 patient populations, route of contrast media administration, and contrast media volumes (Fig. 1). In fact, subjects who undergo coronary angiography and intervention often have a higher burden of comorbidities and are frequently more critically ill than those who undergo computed tomography imaging: diabetes, advanced CKD, heart failure, cardiogenic shock, and ACS are commonly encountered in patients who undergo PCI and have been independently associated with a higher risk of CI-AKI.[14] Additionally, intra-arterial as opposed to intravenous contrast media administration has been linked to a higher risk of CI-AKI, although the exact underlying mechanisms are poorly understood.[16,17] These might involve direct toxic effects by undiluted contrast media reaching the nephrons, but are possibly compounded by concomitant alternative causes of AKI during cardiac catheterization, such as hypotension, microshowers of atheroemboli to the renal arteries, and bleeding.[1,17] Indirect support for this concept has been presented by radial artery access studies, which have reported lower rates of CI-AKI with radial as opposed to femoral access[18] (with radial access the abdominal aorta and renal